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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/765,614	01/22/2001	Jo Klaveness	REF/Klaveness/054C	9751

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EXAMINER

HARTLEY, MICHAEL G

ART UNIT	PAPER NUMBER
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1616

DATE MAILED: 07/09/2002

13

Please find below and/or attached an Office communication concerning this application or proceeding.

**Office Action Summary**

Applicati n No.

09/765,614

Applicant(s)

KLAVENESS ET AL.

Examiner

Michael G. Hartley

Art Unit

1616

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 22 May 2002.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 38-64 is/are pending in the application.
- 4a) Of the above claim(s) 39,45,46,50-62 and 64 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 38,40-44,47-49 and 63 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on \_\_\_\_\_ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

- 13) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☒ Certified copies of the priority documents have been received in Application No. 08/958,993.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 1.5, 12.
- 4) ☐ Interview Summary (PTO-413) Paper No(s). \_\_\_\_\_
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: \_\_\_\_\_

Art Unit: 1616

***Election/Restrictions***

Applicant's election of the species wherein the composition comprises perfluorobutane gas and an anti-CD34 antibody as a targeting agent coupled through thiolated groups in Paper No. 11 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 39, 45, 46, 50-62 and 64 have been withdrawn as not being directed to the elected invention (i.e., are not drawn to the elected species). All other claims have been examined to the extent they read on the elected species.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 38, 40-44, 47-49 and 63 are rejected under 35 U.S.C. 103(a) as being unpatentable over either one of Quay (EP 727225) or Unger (US 5,997,898) in view of Schneider (US 5,643,553) and Martin (US 5,891,468).

Quay discloses compositions comprising a diagnostic and/or therapeutic agent comprising an aqueous suspension of gas-filled microbubbles (a reporter) stabilized by a film-forming surfactant, wherein the agent further comprises a vector (i.e., a targeting molecule), see abstract and page 3+. Quay teaches that the microbubbles may comprise various surfactants (e.g., lipids, etc.) to provide increased stability, which include charged surfactants, see page 4, lines 26-29 and page 27+. The microbubbles are conjugated to various targeting molecules (e.g., antibodies, etc.) to provide the advantage of increased microbubble stability and site-specificity (e.g., pages 4-8) and are bound thereto via a linker (i.e., a covalent or non-covalent tether), see page 8, lines 41-43. Quay further teaches that the gasbubbles may comprise various gases, such as, C<sub>1</sub>-C<sub>5</sub> perfluorocarbons which would include

Art Unit: 1616

perfluorobutane, applicant's elected species, see page 3, lines 54, (note, decafluorobutane is perfluorobutane) and page 9, line 2. The bubbles may also contain a therapeutic agent, see page 6, lines 56+. Quay further teaches that targeting to CD34 is desired, see page 7, lines 33.

Unger discloses a diagnostic and/or therapeutic agent comprising gas-filled vesicles (i.e., microbubbles) stabilized by one or more monolayers of lipid surfactants, including phospholipids (as claimed) and charged surfactants, see abstract, column 5, lines 13-50 and column 21, lines 6+. The microbubbles may comprise various targeting agents (or vectors), including antibodies which are linked to the microbubbles via a thiol moiety (e.g., applicant's elected linker), see column 12, lines 36-49. The microbubbles preferably contain a perfluorocarbon as the gas, including perfluorobutane, see column 15, line 15. The microbubbles may additionally contain a therapeutic agent, see column 6, lines 25+.

Quay and Unger fail to specifically disclose the conjugation of antibodies to phospholipid membranes via a thiolated groups as claimed.

Schneider discloses a diagnostic and/or therapeutic agent comprising gas-filled phospholipid microbubbles (e.g., including charged phospholipids), see abstract and column 6, lines 25+. Schneider teaches that targeting agents (e.g., polypeptides, antibodies, etc.) may be bound to the stabilizing phospholipid surfactant layer of the microbubbles via thiol groups on the antibody to provide site-specific targeting of the diagnostic or therapeutic microbubbles, see column 9, lines 10+.

Martin discloses a composition comprising lipid vesicles that are used for the delivery of diagnostic or therapeutic agents, see abstract. Martin discloses that the liposomes shell may be formed from a phospholipid, (e.g., PE, etc.) see columns 7-8. Martin teaches that the targeting ligand is bound a linker (i.e., a polymer chain) by the use of a functional group, such as a thiolated group, and that the use of such functional groups provides a standard means of coupling antibodies to liposomes see column 15, lines 55+. Martin also teaches that the various targeting agents may be used in an equivalent manner, including anti-CD34 antibodies, which provide the advantage of targeting bone marrow stem cells, see table 1, columns 11-12.

It would have been obvious to one of ordinary skill in the art to use a thiolated moiety to couple the targeting agents to the ultrasound contrast agents comprising a lipid shell as disclosed by Quay or

Art Unit: 1616

Unger because the use of such a coupling means is well known in the art as providing a reliable and standard means of attaching a targeting moiety to phospholipid vesicles to provide increased site-specificity thereof, as shown by Schneider and Martin. Also, it would have been obvious to use a anti-CD34 antibody as the targeting agent in the microbubbles disclosed by Quay and/or Unger because Quay and Unger provide a general teaching that any desirable targeting agent may be employed (e.g., including CD34 as taught by Quay) and the use of an anti-CD34 antibody is known to provide the advantage of specifically targeting bone marrow stem cells, as shown by Martin.

### ***Claim Objections***

Claim 63 is objected to because of the following informalities: Claim 63 recites "bindsto" instead of "binds to" which is a typographical error. Appropriate correction is required.


### ***Conclusion***

No claims are allowed at this time.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael G. Hartley whose telephone number is (703) 308-4411. The examiner can normally be reached on M-F, 7:30-5, off alternative Mondays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jose G. Dees can be reached on (703) 308-4628. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4556 for regular communications and (703) 308-4556 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.

  
Michael G. Hartley  
Primary Examiner  
Art Unit 1616

MH  
July 3, 2002